REMARKS

Claims 1, 6, 8, 9, 11, 12, and 15-22 are pending in the present application.

The rejections of Claims 1-3, 6, 8, 9, and 11-14 under 35 U.S.C. §112, first paragraph (written description and enablement), are obviated by amendment.

This ground of rejection appears to have three distinct parts:

(a) the Examiner alleges that the scope of original claims is too broad with respect to the amino acid sequences embraced therein;

(b) the Examiner alleges that the scope of substrates in the reaction are too broad; and

(c) the term "stringent conditions" is undefined in the original claims and, thus, the Examiner alleges that the scope of homologs is too broad.

With respect to (a), indeed, it is the current trend in U.S. patent examination to narrow the permissible scope of homologs when DNA or protein sequences are claimed. This case falls right in line with this trend.

However, Applicants submit that application of this trend without full evaluation of the nature of the invention and the scope of the disclosure is inappropriate. At the outset, Applicants submit that the most important feature of the present invention is based on the finding that enzymatic reaction of the specific carboxy and amine component as defined in the present claim 1 enables significantly efficient production of a tri- or longer peptide (the peptide is referred to hereinbelow as a"tripeptide" for the sake of simplicity) in the following manner:

$H_2N\text{-}CH(R^1)\text{-}COO\text{-}R + H_2N\text{-}CH(R^2)\text{-}CONH\text{-}CH(R^3)\text{-}COOH \rightarrow$

$H_2N\text{-}CH(R^1)\text{-}CONH\text{-}CH(R^2)\text{-}CONH\text{-}CH(R^3)\text{-}COOH + ROH$ (Formula (A))[1]

A variety of enzymatic methods for producing tripeptides using other substrates (and therefore in other manner than the aforementioned Formula (A)) have already been known in the prior art. One group of such prior-art methods utilizes intracellular protein synthesis enzymes such as aminoacyl-t-RNA synthetase (see US 5,968,787). *In vitro* protein synthetic methods were also developed using the enzyme. But both of the above-mentioned methods require their users to use very expensive raw materials as the raw materials for peptide synthesis. As such, these prior art methods are not appropriate for industrial use.

Another group of the prior-art methods is the enzymatic method for specified products like vibriolysin (EP 0 302 442 A2) or aspartyl-phenylalanine methyl ester (US 4,284,721). In these references, the use of organic solvents for the peptide synthesis is disclosed. But the methods are not applicable for the industrial use either owing to the low reaction yields for the peptide protection and the negative effect of the solvents of the enzymatic activity.

In summary, productivity of any of such prior-art enzymatic methods is far inferior to that of conventional chemical methods. Therefore, none of enzymatic peptide synthesis in the prior art was successfully performed on an industrial scale.

Contrary to such methods in the prior art, the present invention is significantly more efficient and therefore enables production of tripeptides on an industrial scale with an enzymatic reaction. As such, this method is drastically changing the industry of the peptide

[1] Formula (A) is an example representing where all amino acid residues are alpha amino acids, wherein the carboxy component is an amino acid ester, and wherein the amine component is an unprotected dipeptide. Although this reaction is a typical one, the present invention is not limited thereto.

production. Thus the selection of the substrate (i.e., the specific carboxy and amine component) itself is a great novel feature of the present invention.

Since the selection of the substrate in the present Claim 1 is such an important feature, this feature alone can well define an epoch-making invention in the industry. Therefore, regardless of the broadness of the definition of the enzyme, the present Claim 1 should be is to be allowed in its current form.

More specifically, the Examiner is reminded of MPEP § 2163.02, which states:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Applicants refer to page 4, lines 10-15 and page 15, line 15 to page 39, line 1, which provides exhaustive detail as to the nature and identity of suitable enzymes to be used in the present invention, as well as methods of cloning, expressing, and purifying the same. As such, Applicants submit that the specification provides an adequate description to allow the skilled artisan to recognize what has been invented and what is claimed is adequately described in the specification within the meaning of 35 U.S.C. § 112, first paragraph.

MPEP § 2164.01 states:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Applicants submit that determining what sequences fall within or without the scope of the presently claimed invention be readily apparent to the skilled artisan. At page 15, line 15 to page 39, line 1, Applicants provide a detailed example of how the skilled artisan may

clone, express, and characterize any sequence variant to assess its standing with respect to the claimed invention.

In fact, MPEP §2164.06 states:

> ... quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'

Applicants submit that, with the present specification in hand, determination of sequences that fall within the scope of the presently claimed invention would require nothing more than routine experimentation to determine sequence homology and protein activity. As such, Applicants submit that the claims are fully enabled within the context of 35 U.S.C. §112, first paragraph.

With respect to new Claims 16 and 18, Applicants wish to direct the Examiner's attention to a recent decision by the U.S. PTO's Board of Patent Appeals and Interferences (*Ex parte Bandman*, **enclosed herewith)** in which the Board held that claims to amino acid sequences that are at least 95% homologous to the disclosed sequence are adequately described and enabled when the specification describes the nucleotide and amino acid sequences.

As in *Ex parte Bandman*, the present specification provides the amino acid sequence (SEQ ID NO: 12) and the corresponding polynucleotide sequence (SEQ ID NO: 11). Applicants note that the claims have been amended to define the scope of homologs that were previously objected to (now appearing as new Claims 16 and 18) as being one to ten

substitution, deletion, insertion, and/or addition. Applicants note that SEQ ID NO: 12 is a 619 amino acid protein (see SEQ ID NO: 12). As such, the scope of defined homology is 98.3%. Clearly if the Board finds that under similar circumstances to the present specification an amino acid sequence having at least 95% homology is adequately described and enabled, the certainly so too is a homolog that is at least 98.3% homolgous.

Accordingly, the specification adequately meets the current standard of the Office and Applicants should be entitled to sequences that differ from SEQ ID NO: 12 by the recited one to ten amino acids. Therefore, the scope of homologs are described and enabled within the context of 35 U.S.C. §112, first paragraph.

In regard to criticism (b), the Examiner alleges that specification does not sufficiently describe or enable the use of the claimed invention with any amino component and any carboxy component as originally claimed. Applicants disagree with this allegation, but to expedite examination have amended the claims to limit the scope of the substrates as follows. The carboxy component has now been limited to an amino acid ester (such as an alpha amino acid ester H_2N-CH(-R)-COO-R') or an amino acid amide (such as an alpha amino acid amide H_2N-CH(-R)-NH_2), while the amine component has been limited to an unprotected peptide having two or more amino acid residues, a C-protected peptide having two or more amino acid residues, and a peptide having two or more amino acid residues and having a C-terminal amine in place of an amino acid.

Support for the description and enablement of these specifically defined substrates can be found on page 13, line 15 to page 15, line 13 and the Examples. With respect to the Examples, specific mention is made of Tables 13, 16, and 18 where the utility and enablement of several of compounds within the scope of the currently claimed substrates are demonstrated. Specifically, the Examples of the present specification demonstrate a large

variety of tripeptide-producing reactions and dipeptide-producing reactions. This demonstration of such a large variety of reaction sis sufficient to conclude that any amino acid ester or amino acid amide can be used as the carboxy component with the claimed genus of amine components. Even though the dipeptide-producing reaction is not within the scope of the claimed invention, the results demonstrated in the Examples (see Tables 5-10, 12, 13, 15, 16, 17-1, 17-2, 17-3, 17-4, and 18) for dipeptide-producing reactions further support the substrate-specificity as presently claimed.

Moreover, Applicants submit that based on the description provided in the specification, the details and experimental protocols outlined in the Examples, and the results set forth in the Examples, the skilled artisan would be readily be able to appreciate and practice the full scope of the presently claimed invention without undue experimentation. As such, Applicants submit that scope of currently claimed substrates are sufficiently described and enabled within the context of 35 U.S.C. §112, first paragraph.

Finally, to address criticism (c), Applicants have introduced a definition into Claims 11, 13, 20, and 22 of the stringent conditions based on page 27 of the specification. In view of this amendment and the disclosure in the specification, Applicants submit that hybridization stringency and the resulting products are sufficiently described and enabled within the context of 35 U.S.C. §112, first paragraph.

In view of the present amendments, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 6, 8, 11, and 13 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

Applicants have amended the claims herein to address the Examiner's specific criticisms. For example, the amended claims now define the term "stringent conditions" and do not recite the term "inversion." As such, this ground of rejection is no longer believed to be tenable.

Withdrawal of this ground of rejection is requested.

The objections to Claims 11 and 13, Claims 6, 8, 11, and 13, and Claim 2, are obviated by amendment.

The objected to claims have been amended to address the Examiner's specific points of criticism.

Nonetheless, Applicants wish to offer the following explanation with respect to original Claim 2. The Examiner alleges that it is not clear whether the microbe or the enzyme uses as substrates an amine component and a carboxy component. As explained throughout the specification, the enzyme uses the amine component and the carboxy component. However, Applicants submit that the enzyme may be used as an enzyme in isolation or as a product of a certain microbe. The form of the enzyme in the reaction system does not specifically matter, so long as the enzyme is present and able to catalyze the reaction. For example, as stated in original Claim 2, the enzyme may be present in a microbe in a reaction system, may be present in the reaction system as a component of a disrupted or lysed product of the microbe, or may be present in the reaction system as a purified enzyme.

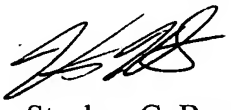
Withdrawal of this ground of objection is requested.

Finally, Applicants acknowledge the Examiner's indication that the specification has not been checked for all possible minor errors. Applicants are unaware of any errors requiring correction.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Stephen G. Baxter, Ph.D.
Registration No. 32,884

Vincent K. Shier, Ph.D.
Registration No. 50,552

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)